



UNITED STATES DEPARTMENT OF COMMERCE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/252,710 06/02/94 RIVIERE

I 8141113

ELLIOTT, G. EXAMINER

18N2/0417

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ART UNIT	PAPER NUMBER
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1805
DATE MAILED:

12
04/17/96

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

08/252,710

Applicant(s)

Riviere et al.

Examiner

George C. Elliott, Ph.D.

Group Art Unit

1805



☒ Responsive to communication(s) filed on Nov 20, 1995

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-4, 6-31, and 35-37 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-4, 6-31, and 35-37 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Part III DETAILED ACTION

1. The provisional rejection of claims 5, 6 and 15 under 35 U.S.C. § 101 as claiming the same invention as claims 24, 6 and 15 of application Serial No. 07/786,015 is withdrawn in view of the abandonment of application Serial No. 07/786,015.
2. The provisional rejection of claims 5, 6 and 15 under 35 U.S.C. 102(e) as being anticipated by copending application Serial No. 07/786,015 which has a common inventor with the instant application is withdrawn in view of the abandonment of application Serial No. 07/786,015.

Double Patenting

3. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-4 and 6-8 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting

as being unpatentable over claims 1-3 of copending application Serial No. 08/486,858. Although the conflicting claims are not identical, they are not patentably distinct from each other because the vectors claimed in the copending application contain essentially the same components as those claimed in the instant application.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

6. Claims 1-4, 6-8, 20, 21 and 35-37 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin in view of Bender et al. and Cone et al. Temin teaches the construction of various defective recombinant retroviral vectors based on murine leukemia viruses. These vectors can express a gene of interest, which may be virtually any gene because, as noted at page 163, there "are no reports of genes that cannot be expressed in retrovirus vectors." Helper cells transduced with these vectors are taught on page 156 of Temin. Temin further teaches that retroviral vectors may employ splice donor and acceptor sites (see page 162, constructs 5-7). Temin also teaches that stocks of helper-free virus may be prepared from vectors that do not have a selectable marker if the vectors are cotransfected into helper cells with a plasmid containing a selectable marker. Cone et al. teach the construction of helper-free recombinant retroviral vectors and note on page 6353 that:

"...one can readily isolate lines such as Ψ-AM2275 that produce $>10^5$ recombinant virus per ml. These titers are high enough to facilitate the nonselective introduction of genes into 100% of a population of cells at high enough cell numbers to allow rapid analysis of DNA, RNA, or protein."

The claims are drawn to vectors that have splice donor and acceptor sites located between a 5' LTR and a 3' LTR and do not contain complete *gag*, *pol* or *env* genes or a complete selectable marker. One of ordinary skill in the art would have known from

the combined teachings to make recombinant retroviral vectors that lack a complete selectable marker since the selectable marker gene would be unnecessary in view of the teaching of Cone et al. Therefore, the invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

7. Claims 2-4 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin in view of Cone et al. as applied to claims 1, 6-8, 20 and 21 above, and further in view of Bender et al. Bender et al. teach that the packaging signal of vectors based on Moloney murine leukemia virus extends into the *gag* region. Claims 2-4 and 20 as it depends from 2-4 are drawn to vectors as above that also include a portion of the *gag* gene to enhance packaging. One of ordinary skill in the art would have known from the combined teachings to modify the recombinant retroviral vectors suggested by Temin and Cone et al. by including a portion of the *gag* gene to ensure efficient packaging as suggested by Bender et al. Therefore, the invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

8. Claims 9 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin in view of Cone et al. as applied to claims 1, 6-8, 20 and 21 above, and further in view of Kenten et al. or Kuo et al. Temin and Cone et al. are described *supra*. Kenten et al. describe the construction of various plasmid vectors for expression of foreign genes in myeloma cell lines.

The reference demonstrates the vector-mediated transfer of the gene for tissue plasminogen activator (tPA), under the control of a retroviral LTR promoter, into mammalian cells. Kuo et al. describe the cloning and expression in *E. coli* of Factor VIIIC. At page 34, the transfer of the gene into mammalian cells by way of retroviral vectors is suggested. Claims 9 and 20 as it depends from claim 9 are drawn to retroviral vectors carrying genes for factor VIII or tPA. The combined teachings of the prior art suggest the usefulness of expression of these proteins in mammalian cells in culture. The prior art of either Kenten et al. or Kuo et al. suggest expression of such genes by vector mediated gene transfer. The use of retroviral vectors would have been obvious, especially in view of the suggestions of Kenten et al. and Kuo et al. to use retroviral LTRs as promoters and the statement by Temin, cited above, that there "are no reports of genes that cannot be expressed in retrovirus vectors." Therefore the invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

9. Claims 10, 11, 17, 18 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin in view of Cone et al. as applied to claims 1, 6-8, 20 and 21 above, and further in view of Emerman et al. Temin and Cone et al. are described *supra*. Emerman et al. describe the construction of retroviral vectors in which an internal heterologous α -globin promoter and 5' untranslated region is used to express the heterologous thymidine

kinase gene. Claims 10, 11, 17, 18 and 20 as it depends from any of the preceding, are drawn to recombinant retroviral vectors which contain the α -globin promoter and 5' untranslated region. Emerman et al. teach the use of such a promoter construct to express a heterologous gene from a retroviral vector. It would have been obvious to one of ordinary skill in the art to use such promoter constructs in the vectors of Temin, given the combined teachings of the prior art.

10. Claims 16 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin in view of Cone et al. and Emerman et al. as applied to claims 10, 11, 17, 18 and 20 above, and further in view of Yee et al. or Yu et al. Temin, Cone et al. and Emerman et al. are as described above. Yee et al. and Yu et al. describe the modification of retroviral vectors for the purpose of deleting the 3' LTR enhancer or promoter sequences. These vectors are termed "disabled retroviral vectors" or "self-inactivating retroviral vectors". The intent is to prevent the activation of downstream genes by the 3' LTR when the retrovirus inserts into the host genome. Or, the inactivated elements may transfer to the 5' LTR, inactivating the enhancer in the 5' LTR, and thereby allowing regulated expression of a heterologous gene from an internal promoter without interference by expression from an active 5' LTR. Claims 16 and 20 as it depends from 20 are drawn to further modifications of the retroviral vectors of the instant application such that the retroviral enhancer element is

inactivated such that the α -globin gene promoter controls the expression of the inserted heterologous gene. Given the combined teachings of the prior art, inactivation of the retroviral enhancer would have been obvious for allowing specific expression through the heterologous promoter.

11. Claim 19 is rejected under 35 U.S.C. § 103 as being unpatentable over Temin in view of Cone et al. and Emerman et al. as applied to claims 10, 11, 17, 18 and 20 above, and further in view of Kenten et al. or Kuo et al. Temin, Cone et al., Emerman et al., Kenten et al. and Kuo et al. are as described above. Claim 19 is drawn to retroviral vectors which express either factor VIII or tPA. For essentially the same reasons as set forth hereinabove, the combined teachings of the prior art teaches the importance of expressing these proteins. It would have been obvious to express either factor VIII or tPA by way of such retroviral vectors.

12. Claims 12-15, 20 and 22 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin in view of Cone et al. and Emerman et al. as applied to claims 10, 11, 17, 18 and 20 above, and further in view of Anderson and deVilliers. The teachings of Temin, Cone et al. and Emerman et al. are as described above. Anderson describes retroviral vectors for expression of exogenous genes. On pages 405-407, methods for optimizing and modifying the expression of exogenous genes are noted. In particular, the use of exogenous enhancers is described therein. deVilliers

describes in Column 1, lines 32-53, the use of enhancers, specifically the CMV enhancer, to optimize the expression of exogenous genes inserted into vectors. Claims 12-15, 20 as it depends from 12-15, and 22 are drawn to retroviral vectors in which an exogenous enhancer is included to express heterologous genes. The combined teachings of the prior art suggest the use of exogenous enhancers, and particularly the CMV enhancer, for the same purpose. It would have been obvious to include such enhancers for this purpose.

13. Claim 22 is rejected under 35 U.S.C. § 103 as being unpatentable over Temin in view of Cone et al. as applied to claims 1, 6-8, 20 and 21 above, and further in view of Anderson or deVilliers. The teachings of Temin, Cone et al., Anderson and deVilliers are as presented above. Claim 22 is drawn to a defective recombinant retroviral vector based on a murine leukemia virus, wherein the vector contains an exogenous enhancer. For the reasons set forth above, the use of exogenous enhancers as suggested by Anderson or deVilliers in the vectors of Temin taken with Cone et al. would have been obvious.

14. Claims 23 and 24 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin in view of Cone et al., Anderson and deVilliers as applied to claim 22 above, and further in view of Hilberg et al. or Holland et al. The teachings of Temin, Cone et al., Anderson and deVilliers are as presented above. Hilberg et al. teach that retroviral vectors based upon Moloney murine

leukemia virus (MuLV) may be generated which contain the enhancer region from a myeloproliferative sarcoma virus (MPSV) mutant. Substitution of this enhancer in the vectors of Temin taken with Cone et al. would have been obvious, particularly in view of the teaching that the use of the MPSV enhancer allows expression of the viral vector genome in embryonal carcinoma cells, a developmental cell line. Holland et al. teach that retroviral vectors based upon Moloney murine leukemia virus (MuLV) may be generated which contain the enhancer region from Friend murine leukemia virus (Fr-MuLV). Substitution of this enhancer in the vectors of Temin taken with Cone et al. would have been obvious, particularly in view of the teaching that the use of the Fr-MuLV enhancer allows expression of the viral vector genome in hematopoietic progenitor cells.

15. Claims 25-31 are rejected under 35 U.S.C. § 103 as being unpatentable over Temin in view of Cone et al., Anderson and deVilliers taken with either Hilberg et al. or Holland et al. as applied to claims 23 and 24 above, and further in view of either Franz et al. or Weiher et al. Temin, Cone et al., Anderson, deVilliers, Hilberg et al. and Holland et al. are as described *supra*. Weiher et al. teach that the B2 mutation of MuLV vectors works synergistically with the enhancer element and allows for enhanced RNA stability in certain cells, such as F9 cells. The discussion suggests that the B2 mutation may affect the efficiency of translation as well. Inclusion of the B2

mutation in the vectors of Temin taken with Cone et al., Anderson, deVilliers and either Hilberg et al. or Holland et al. would have been obvious as a means of increasing gene expression with these vectors. Franz et al. teach that retroviral vectors using MPSV LTRs can result in expanded host range of the vectors, especially in efficient transduction of embryonic cells. Inclusion of these LTR elements would have been obvious as a means of increasing the host range of the MuLV based vectors.

Response to Amendment

16. Applicant's arguments filed November 20, 1995 have been fully considered but they are not deemed to be persuasive. Applicant's arguments in response to the rejections over prior art rely almost entirely on Applicant's assertion that the prior art does not teach recombinant retroviral vectors that lack a selectable marker gene. As presently amended, all outstanding claims now recite vectors that do not include a complete gene for a selectable marker. Applicant's attempt to dismiss the teachings of Cone et al. regarding retroviral vectors without marker genes is unpersuasive. First, Applicant refers to the Cone et al. statement as "a conclusory comment that titers approaching 10^5 per ml might enable the nonselective introduction of genes into 100% of a population of cells." Applicant continues by noting that there is no experimental support for the comment and that it is merely an invitation to experiment. These

comments by Applicant are unpersuasive because the statement by Cone et al. is a direct teaching that titers of $>10^5$ per ml, not "approaching 10^5 per ml", are produced and that these are high enough to facilitate nonselective introduction of virus into 100% of the cells, not that they might enable such a result. Cone et al. do suggest that retroviral vectors can be used without selection "to allow rapid analysis of DNA, RNA, or protein." One of ordinary skill in the art would recognize that in the absence of a requirement for selection, it would be obvious to use a retroviral vector without a selectable marker gene.

Applicant further asserts that subsequent studies by one of the authors of the Cone et al. reference revealed that Cone's suggested titer is nearly an order of magnitude lower than titers needed to achieve the practical nonselective introduction of genes into mammalian cells. Applicant's assertion is made without supporting evidence and it is well established that assertions made by an attorney in response to a rejection can be afforded little weight in the absence of supporting evidence. Evidence presented by Applicant in a declaration under 37 CFR 1.132 showing a direct comparison of the instant invention to the line Ψ-AM2275 disclosed by Cone et al. may be more dispositive of this issue.

Additionally, Applicant asserts that none of the cited art recognizes the need for novel vectors that efficiently transduce cells without requiring a selection step, and that recognition of

a problem that is previously unrecognized can impart non-obviousness and patentability to a solution to the problem. However, Cone et al. provided a reason for achieving nonselective introduction of genes into whole populations of cells; i.e., that such wholesale introduction allows the rapid analysis of DNA, RNA and protein. Given the teaching of Cone et al. regarding the availability of producer cells that yield a high enough titer to introduce genes into all cells in a population, those of ordinary skill in the art would recognize the redundancy of a selectable marker gene. Thus, while the specific problem asserted by Applicant may not be disclosed in Cone et al., a motivation to obtain nonselective introduction of genes into cells is taught, such that one of ordinary skill in the art would have been motivated to make the claimed invention.

Specification

17. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification remains objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention for the reasons of record in the

last Office action as they pertain to the description of Figure 11. Applicant's amendment to the specification substituting filled in blocks for the empty blocks in the description of Figure 11 has not been entered because the Office does not have the means to accurately make the required changes. It is suggested that Applicant submit substitute pages with the boxes filled in with the appropriate shading. However, it is also noted that the proposed changes would be considered new matter unless Applicant can point to clear and unambiguous support for the correspondence between the shading in the blocks associated with the various vector segments and regions in the description and the shading in the vector representations in Figure 11.

Claim Rejections - 35 USC § 112

18. Claims 1-31 and 35-37 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Conclusion

19. No claim is allowed.

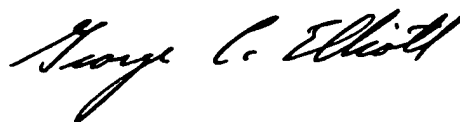
20. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

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A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to George Elliott, Ph.D. whose telephone number is (703) 308-4003.



Elliott
March 18, 1996

GEORGE C. ELLIOTT
PRIMARY EXAMINER
GROUP 1800